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(54) Title: MEDICAMENTS CONTAINING DEXTRIN FOR TREATING RESPIRATORY DISORDERS SUCH AS CYSTIC FIBROSIS

(57) Abstract: There is described a pharmaceutical composition suitable for the treatment of a respiratory disorder comprising an effective amount of dextrin. There is also described a method of treating a respiratory disorder which comprises the administering of a therapeutically effective amount of dextrin to a patient suffering from such a disorder.

MEDICAMENTS CONTAINING DEXTRIN FOR TREATING RESPIRATORY DISORDERS SUCH AS CYSTIC FIBROSIS

This invention relates to a novel form of medicament, novel formulations comprising the medicament and novel methods of treatment.

Cystic fibrosis (CF) is characterised by overproduction of adherent, highly viscous, pulmonary mucus secretions. It is a genetically determined disease with 0.05% prevalence among US Caucasian children, that predisposes sufferers to fatal respiratory infections. CFTR gene mutations lead to reduced chloride ion secretion and hence reduced water secretion. Although the pathology of the over production of highly viscous pulmonary mucus secretions is not clearly understood, it is postulated that the underlying mechanism is due to;

a) defects in chloride secretion; and/or
b) hyperabsorption of sodium (and water) leading to decreased fluid on the airway surface

The CF gene, identified in 1989, encodes a c-AMP-mediated chloride channel (CFTR) situated in the apical membrane of epithelial cells, including the epithelial lining of the airways. Mutations in the gene results in either absent or dysfunctional CFTR protein with consequent impairment of ion transport across these cells ie. impaired chloride secretion and increased sodium absorption. A number of hypotheses attempt to link defects in CFTR-mediated ion transport to CF lung disease. The 'low volume' hypothesis postulates that compared to normal airway surface liquid (ASL) which has salt levels approximately equal to plasma, CF ASL is depleted of salt because of the faulty CFTR. Thus, abnormally elevated isotonic fluid absorption depletes the ASL, leading to impaired mucociliary clearance, a failure to clear thickened mucus from the airway surface and likely, the initiation of chronic infection. This hypothesis raises the possibility that the disease will best be managed by therapy directed at restoring the volume (salt and water) composition on airway surfaces.

CONFIRMATION COPY

It has been shown (Robinson et al. Eur Respir J 1999; 14; 678-685) that mannitol or hypertonic saline is useful in affecting the clinical benefit of surrogate markers in CF. This is believed to be because of its effect on water transport. However, since the relatively small mannitol molecules (Molecular Mass 182) are readily absorbed, the duration of action is limited.

International Patent Application No WO 95/22993 describes the use of sugars such as mannitol and/or dextrose (also known as glucose) as an osmolarity changing agent. The use of mannitol suffers from the disadvantage that, *inter alia,* in the presence of various *Pseudomonas aeruginosa* exoproducts, the permeability of cell monolayers to mannitol increases. Thus the presence of an abundance of Pseudomonas exoproducts, for example, in CF sputum, increases the permeability of the airway epithelium and therefore decreases the effectiveness of mannitol.

US Patent No 5,925,334 describes the use of phospholipid surfactants to promote mucus clearance. However, the use of such phospholipid surfactants is disadvantageous in that, *inter alia*, the medicament tends to be very expensive.

International Patent Application No WO 95/17898 describes a method of preventing infections by bacterial pathogens, in particular reducing the risk of infection by *P. aeruginosa*, which is the predominant respiratory tract pathogen in patients with cystic fibrosis. The method comprises the administration of dextran directed towards the buccal cavity.

International Patent Application No WO 99/01141 describes the use of dextran to reduce the viscoelasticity and increase mucus clearance of sputum of cystic fibrosis patients. The dextran being administered by a nebuliser or via an endotracheal tube as a solution with a concentration of from 4mg/ml to 40mg/ml.

More recently, International Patent Application No WO 01/15672, which was published on 8 March 2001, described the use of dextran sulphate as improved mucoactive agent which improves viscoelasticity and clearance of respiratory tract mucus. The dextran sulphate was preferably administered as an aerosol eg from a nebuliser, although administration via a dry powder inhaler was contemplated.

We have now surprisingly found that dextrin may overcome or mitigate the disadvantages of the prior art approaches and may be able to improve mucus clearance when administered directly into the respiratory tract of a patient.

Dextrin is a 1,4-polyglucose material as distinct from dextran which is a 1,6-polyglucose. Dextrins are known from European Patent Applications No 0 115 911 and No 0 153 164 to be useful in peritoneal dialysis. To achieve peritoneal dialysis dextrins are generally administered into the peritoneal cavity as a modified, iso-osmotic 7.5% w/w aqueous solution.

Thus, according to the invention we provide a pharmaceutical composition suitable for the treatment of respiratory disorders comprising an effective amount of dextrin.

A variety of dextrins may be used in the composition of the invention provided that the osmotic properties of the polymer are appropriate to promote water absorption and have a suitable duration of action due, *inter alia*, to their limited absorption.

Preferred polymers are therefore the 1,4-glucose polymers or a mixture of dextrin glucose polymers. Especially preferred are those dextrin polymers described in European Patent Applications No 1 115 911 and No 0 153 164. Dextrins are preferred, inter alia, because if they are absorbed they are readily metabolised to oligosaccharides and ultimately glucose, which is in contrast to dextrans.

Therefore, according to a preferred embodiment of the invention we provide a pharmaceutical composition as hereinbefore described comprising a dextrin polymer

mixture, said mixture including more than 15% by weight of glucose polymers with a degree of polymerisation greater than 12, preferably 50% by weight of glucose polymers with a degree of polymerisation (D.P.) of greater than 12.

The mixture may contain from 50 to 90% by weight of glucose polymers of D.P. greater than 12. It is advantageous to use a mixture containing from 75 to 100%, preferably 90 to 100%, by weight of glucose polymers of D.P. greater than 12. It is preferred that the weight average molecular weight (Mw) is in the range of from 3,000 to 75,000. More preferably, the Mw is from 3,000 to 50,000 and most preferably from 5,000 to 50,000. The Mw of the polymer mixture is especially preferred to be in the range from 15,000 to 25,000 and more especially 18,000 to 22,000 (as determined by either high pressure liquid chromatography or size exclusion chromatography). It is particularly desirable that the content of oligosaccharides in the glucose polymer mixture should be kept at a low level to reduce absorption. The oligosaccharide content of the glucose polymer mixture should be no higher than 10% by weight, the mixture containing from 90 to 100% by weight of glucose polymers of D.P. greater than 12.

The dextrin polymer (as obtained by the hydrolysis of starch), may be in the form of either unsubstituted dextrin or may be substituted by one or more different groups. The substituents may be negatively charged groups, for instance, sulphate groups, neutral groups, or positively charged groups, for instance, quaternary ammonium groups. In the case where the substituent group is sulphate, it is preferred that the sulphated dextrin contains at least one sulphate group per saccharide (glucose) unit.

Dextrin is a mixture of polymers of glucose and the glucose units may be substituted in one or more of the 2, 3 and 6 positions by sulphate groups and the position of such sulphate groups may vary.

A dextrin sulphate of use in the present invention may have up to 2, 3 and 6 positions by sulphate groups.

A dextrin sulphate of use in the present invention may have up to two sulphate groups per glucose unit and preferred dextrin sulphates are those having about 1, or between 0.5 and 1.5, preferably up to 1.2, for example 1.1, sulphate groups per glucose unit. More preferably, the agent is the 2- or 6-sulphate of dextrin or a mixture thereof, most preferably dextrin-2-sulphate (D-2-S) that is dextrin wherein a substantial proportion of the sulphate groups are in the 2-position, preferably greater than 75%, more preferably greater than 90%, e.g. 94%.

The dextrin polymer mixtures used in this invention can be produced by hydrolysis of starch in a known manner, followed by treatment of the mixture of glucose polymers so obtained in order to remove some or all of the glucose polymers of lower molecular weight.

A dextrin polymer mixture may be prepared by a variety of methods, including for example, the process described in European Patent Application No 0 115 911 and removal of lower molecular weight polymers is then effected by known fractionation techniques, such as solvent fractionation, or separation of the polymers with the aid of permeable membranes of appropriate cut-off characteristics.

The pharmaceutical composition of the invention may be utilised in the treatment of any respiratory disorders known to result in, *inter alia*, an abnormality in the quantity or quality of the mucus or its clearance. Thus for example the pharmaceutical composition can be useful in the treatment of respiratory disorders such as chronic bronchitis, asthma, bronchiectasis and CF.

In the treatment of respiratory disorders the pharmaceutical composition may be administered in a variety of ways but the most preferred method of administration is by way of inhalation. Thus, the pharmaceutical composition can be administered by way of an inhaler, e.g. a metered dose inhaler or a dry powder inhaler, an insufflator

or nebuliser, or any other conventionally known methods of administering inhalable medicaments.

For use in the treatment of respiratory disorders the compositions of the present invention may be in the form of an aqueous solution which preferably contains at least 0.1% by weight of the glucose polymer mixture, the concentration of which is selected according to the nature of the treatment involved and the needs of the patient. The upper limit of this concentration is subject to keeping the viscosity of the solution low enough that it will pass easily through the inhalation apparatus being used for introducing the medicament into the patient.

When administered by way of inhalation the pharmaceutical composition may be in the form of a pressurised aerosol. Thus, according to a further feature of the invention we provide a pharmaceutical formulation suitable for administration by way of a pressurised aerosol comprising a pharmaceutical composition as hereinbefore described in admixture with at least a suitable propellant and optionally with a surfactant or a mixture of surfactants. The propellant is preferably a non-CFC propellant, such as a hydrofluoroalkane (HFA). Any conventionally known HFA propellant may be used, however, HFAs which may be mentioned include a fluoroalkane such as a fluoromethane or a fluoroethane or a mixture of fluoroalkanes. Such fluoroalkanes include, but are not limited to, trichlorofluoromethane, dichlorodifluoromethane, 1,2-dichlorotetrafluorethane, trichlorotrifluoroethane and chloropentafluoroethane, HFA 227 or HFA 134 (1,1,1,2-tetrafluoroethane). The amount of propellant present may vary, but generally the pharmaceutical composition to propellant ratio will be from 1 to 300 to 1 to 5. Mixtures of propellants may be used, for example, a mixture of HFA 134 and HFA 227. The aerosol composition of the invention may be present as a solution or a suspension of the active ingredient with a propellant.

The pressurised aerosol formulation of the invention may be administered in any conventionally known inhalation apparatus.

In another embodiment the pharmaceutical composition may be administered as a dry powder formulation. The composition may be administered with or without an adjuvant, diluent or carrier. However, according to the invention we provide a pharmaceutical formulation suitable for administration by way of a dry powder inhaler comprising a pharmaceutical composition as hereinbefore described in admixture with a suitable adjuvant, diluent or carrier. Any conventionally used ingredients in dry powder formulations may be used, such as sugars, which include, but are not limited to, dextran and lactose, eg crystalline lactose. Preferably, when a carrier is used the pharmaceutical composition to carrier ratio is from 0.01:50 to 1:1.

The dry powder formulation of the invention may be administered in any conventionally known inhalation apparatus. However, preferred apparatus are those commercially available as CLICKHALER (described in International Patent Application No WO92/00771) and/or TECHNOHALER (described in International Patent Application No WO93/16748).

The dry powder formulation of the invention may comprise microcapsules consisting of a biocompatible wall material encapsulating the medicament. Thus, for example, the wall material may encapsulate only the polymeric osmotic agent or a mixture of a polymeric osmotic agent and a pharmaceutically acceptable adjuvant, diluent or carrier. Similar microcapsules are described in US Patent No. 5,384,133 which is incorporated herein by reference. Thus suitable wall materials include, but are not limited to, polymeric materials, such as, poly (glycolic acid), poly-d,1-lactic acid copolymers thereof, copolyoxalates, polycaprolactone, poly(lactic acid-caprolactone), and the like.

Alternatively, the formulation may be administered by way of a conventional nebuliser. A suitable nebuliser formulation consists of a sterile solution of a pharmaceutical composition of the invention in water, optionally containing one or more surfactants or a pharmaceutically acceptable co-solvent and agents to render the

solution isotonic. Alternatively, the nebuliser formulation may comprise a suspension of a pharmaceutical composition of the invention in finely divided form in a sterile solution. The solution or suspension may be nebulised by an air jet, dropping onto an ultrasonic vibrating plate, forcing through small orifices or other known types of nebuliser, including unit-dose nebulisers, including those described by Dolovich, M., "New Propellant-free Technologies under Investigation", J. Aerosol Medicine, 1999; 12 (suppl 1): S9-S17, such as, Respimat (from Boehringer Ingelheim), AERx™ (from Aradigm), and AeroDose (from Aerogen).

For inhalation therapy the pharmaceutical composition is preferably micronised. The particle size of the polymer may vary. However, it is preferred that the particles will have a particle size of 10 microns or less.

The dosage of pharmaceutical composition administered to a patient may vary depending, *inter alia*, upon the nature and severity of the disorder being treated and the method of administration. Generally, the amount of the pharmaceutical composition administered is preferably in the range of from 1 mg to 10 g per metered dose or actuation.

In a preferred embodiment, each metered dose or actuation of the inhaler will generally contain from 1 mg to 10 g of the dextrin polymer or mixture of dextrin polymers. The frequency of administration of the pharmaceutical composition of the invention will vary, but most preferably, the pharmaceutical composition will be administered on a daily basis.

According to a further feature of the invention we provide a method of treating a respiratory disorder which comprises the administration of a therapeutically effective amount of dextrin polymer to a patient suffering from such a disorder.

We especially provide a method of treating CF which comprises administering of a therapeutic amount of a dextrin polymer.

We also provide the use of a dextrin polymer in the manufacture of a pharmaceutical composition for the treatment of respiratory disorders.

The inhaled dextrin of the invention may be administered in conjunction with a variety of other medicaments, simultaneously, sequentially or separately.

Other medicaments which may be mentioned include medicaments conventionally used in the treatment of asthma and/or bronchitis. Such medicaments include, but are not limited to β_2-agonists, e.g. fenoterol, formoterol, pirbuterol, reproterol, rimiterol, salbutamol, salmeterol and terbutaline; non-selective beta-stimulants such as isoprenaline; xanthine bronchodilators, e.g. theophylline, aminophylline and choline theophyllinate; anticholinergics, e.g. ipratropium bromide; bronchial anti-inflammatory agents, e.g. nedocromil sodium; and steroids, e.g. beclomethasone diproprionate, fluticasone, budesonide and flunisolide; and combinations thereof.

Other medicaments which may be mentioned include; general expectorants, decongestants, and mucolytics; and CF-specific therapies; such as recombinant human DNase (dornase alfa/rhDNase), inhibitors of sodium ion absorption (e.g. the sodium channel blocker, amiloride), inducers of chloride ion secretion (e.g. the triphosphate nucleosides, ATP and UTP) and conventionally known antibiotics, dopamine agonists, e.g. sibenadet and α-1 antitrypsin.

The invention will now be described by way of example only.

Example 1

Preparation of a Dextrin Solution

A solution containing 200mg/ml dextrin (in which more than 50% by weight of glucose polymers have a DP of greater than 12) in water was prepared and 5ml

placed in a Pari LC Plus nebuliser (Pari GmbH, Germany) and operated with a Pariboy air compressor at 6 litres/minute. The nebuliser was connected to a Pari Sinus Breathing Simulator set to a tidal volume of 600 ml, 12 breaths per minute, inspiratory fraction 40% generating a minute volume of 7.2 litres, a maximum inspiratory flow of 28.3 litres/minute and a mean inspiratory flow of 18 litres/minute, in order to simulate the effect of a patient breathing from the nebuliser. In 15 minutes the mean mass of solution nebulised was 2.1g. More than 95% of the dextrin was recovered from the apparatus. A mean of 151mg was detected on the inspiratory filter indicating that this quantity would be inhaled by patients.

With a 100 mg/ml solution a mean of 2.9g of solution was nebulised in 15 minutes and 126 mg recovered on the inspiratory filter.

Use of a Ventstream nebuliser with Portaneb compressor gave broadly similar results.

When icodextrin 200 mg/ml was prepared in 0.9% w/v sodium chloride and nebulised with the Pari LC Plus, the quantity of drug recovered from the inspiratory filter was 131 mg, which is not significantly different to the result in solution in water.

The output of droplets from the nebulisers was also evaluated using an Andersen Cascade Impactor operated at 28.3 litres/minute. This allows the particle size distribution of the nebulised droplets to be measured by inertial impaction. With the Pari LC Plus nebuliser and a 200 mg/ml solution, 77% of the droplets were less than 4.7μm in diameter and thus small enough to penetrate the bronchial tree of a patient. With the Ventstream nebuliser 86% of the droplets were less than 4.7μm. These proportions of droplets of respirable size are suitable for patient treatment.

Example 2

A comparison of the effect on bacterial growth was made between mannitol and dextrin.

2.1 Bacteria:

Clinical (CF) strains of mucoid and non-mucoid *P.aeruginosa* (n=6 of each), Staphylococcus aureus, Maltophilia and Burkholderia cepacia were obtained from the department of microbiology, Royal Brompton Hospital

The organisms were taken from stubs, plated out to check purity and then grown up overnight in broth. The bacteria were spun and rediluted at concentrations approximately equivalent to that reported from in patient sputum samples *ex vivo*:

2.2 Icodextrin/Mannitol

Three concentrations: 5 mg/ml, 50 mg/ ml, 250 mg/ml (based on final concentration extrapolated to airway surface liquid (ASL) when nebulising 5 ml of a 200 mg/ml solution (ie. 10% of 1 g reaches small airways, and dissolves in 3 - 3.5 ml of ASL = 100 mg in 3.5 ml) In some cases higher concentrations were also used.

These were made up to double concentrations to account for dilution x 2 using sterile PBS as diluent.

Bacteria were plated, checked for purity and incubated in the presence of icodextrin or mannitol in both PBS and in parallel standard broth. Bacterial growth was quantified and data expressed as % change compared to control samples in which bacteria were incubated in either saline alone or broth alone respectively. The data is shown in Table I and demonstrate that icodextrin had an inhibitory effect while bacteria proliferated in the presence of mannitol.

Example 3

3.1 Measurement of stimulus

This was a two part study:

Part A: Acute effects of inhaled icodextrin on CF patients

In order to assess whether inhaled icodextrin is associated with any acute safety problems (bronchoconstriction or inflammation) in CF patients, nine CF subjects were studied. These were divided into three groups of 3 each, with the first group receiving a dose of 200 mg dextrin (1 ml). The second group received a dose of 600 mg icodextrin (3 ml) and the third group, a dose of 2 g dextrin (10 ml).

Part B: Double blind, placebo-controlled, single dose crossover study

The effects of a single dose of icodextrin or placebo were measured over a period of 24 hours with subsequent follow-up measurements over a 7 day period to exclude safety problems. The same patients were then studied similarly following a single dose of either dextrin or placebo (depending on what was administered first) and the results compared

Subjects and study groups

Part A: Adult patients (age ≥18, n=9) with a confirmed diagnosis of cystic fibrosis and FEV_1 > 60% predicted

Part B: Adult patients (age ≥18, n=10) with a confirmed diagnosis of cystic fibrosis and FEV_1 > 60% predicted.

Participants randomly received either icodextrin or placebo on the first administration, and then the other following a 7-14 day interval.

Treatments were double blinded.

3.2 Drug preparation and administration

Icodextrin was aerosolised using a Pari-LC Plus jet nebuliser. The powder was diluted in normal saline to a concentration of 200 mg/ml under aseptic conditions,

and passed through a 0.2 μm filter directly into the nebuliser. The total dose delivered from the nebuliser was:

Part A: 200 mg (n=3)

600 mg (n=3)

2 g (n=3)

Part B: top safe dose determined by part A (n=10)

Control was an equivalent volume of normal saline, matched with the dextrin solution for osmolarity and approximately for taste.

3.3 End Points

Part A SAFETY:

1) Spirometry: measurements were made prior to icodextrin administration and then at 15 minute intervals for a period of two hours following treatment, and hourly for the following four hours. Measurements were also to be made at home on hand-held digital spirometers and recorded lung function parameters at 12 hours and 24 hours following treatment
2) Blood: Haemotology and biochemical screens including renal and liver function were measured prior to treatment and six hours following treatment.

Part B SAFETY:

The following measurements were made prior to the study (baseline), and repeated at different time as shown in Table 1.

(1) Blood: Haemotology and biochemical screen including renal and liver function, and a series of inflammatory cytokines

(2) Sputum : Microbiology (colony counts); inflammatory cytokines

(3) Pulmonary function (to include full lung function as baseline and at the end of the study with spirometry measured throughout the study)

(4) Imaging: CT chest - A single high resolution slice at each of the upper, middle and lower zones of the lungs at both full inspiration and full expiration were performed at baseline (prior to the intervention) and then again 6 hours and 24 hours after each intervention (ie. on five occasions). This endpoint also provided efficacy information.

3.4 Efficacy

Each patient underwent a baseline study of MCC (in the absence of interventions) 1-2 weeks prior to commencement of the study.

(1) Mucociliary clearance (MCC) was determined by a radioaerosol/gamma camera technique using 5 microns polystyrene particles labelled with ^{99m}Tc. Prior to and immediately after intervention with the test substances, whole lung counts were measured with two collimated scintillation counters. This was followed by half-hourly measurements over a 6 hour period. A final measurement was made 24 hours after intervention to take account of alveolar deposition of labelled particles and a tracheobronchial clearance curve was plotted. Mucociliary clearance was expressed as the area under the tracheobronchial radioaerosol retention curve.

(2) Sputum: rheology, α-amylase

(3) Lung function: Spirometry

(4) CT Scans: As described above, were used to determine whether any change in mucociliary clearance following icodextrin is accompanied by detectable changes in small airway patency.

Table 1

Data % difference compared to control bacteria grown in either saline or broth alone

Icodextrin v Pseudomonas aeruginosa		Mean	se	**Mannitol v Pseudomonas aeruginosa**		Mean	se
Saline				**Saline**			
Non mucoid	5mg/ml	26	24	NM	5mg/ml	93	47
	50mg/ml	4	16		50mg/ml	85	32

	250mg/ml	-11	26		250mg/ml	92	32
Mucoid	5mg/ml	11	11	M	5mg/ml	104	18
	50mg/ml	0	8		50mg/ml	91	31
	250mg/ml	-34	5		250mg/ml	76	35
Broth				**Broth**			
NM	5mg/ml	-2	3	NM	5mg/ml	-3	6
	50mg/ml	-1	5		50mg/ml	-16	9
	250mg/ml	-56	6		250mg/ml	-54	11
M	5mg/ml	5	8	M	5mg/ml	-6	3
	50mg/ml	-5	6		50mg/ml	-14	4
	250mg/ml	-48	4		250mg/ml	-56	6

Icodextrin v Staphylococcus aureus

		Mean	se
Saline			
	5mg/ml	39	54
	50mg/ml	51	46
	250mg/ml	37	34
Broth			
	5mg/ml	5	7
	50mg/ml	-3	6
	250mg/ml	-23	12

Mannitol v Staphylococcus aureus

		Mean	se
Saline			
	5mg/ml	-1	42
	50mg/ml	384	305
	250mg/ml	384	305
Broth			
	5mg/ml	16	7
	50mg/ml	15	11
	250mg/ml	9	8

Icodextrin v Maltophilia

		Mean	se
Saline			
Maltophilia			
	5mg/ml	32	7
	50mg/ml	14	5
	250mg/ml	-53	6
	500mg/ml	-67	5
	750mg/ml	-41	11
Broth			
	5mg/ml	-4	5
	50mg/ml	-5	7
	250mg/ml	-47	7
	500mg/ml	-72	2
	750mg/ml	-78	4

Mannitol v Maltophilia

		Mean	se
Saline			
	5mg/ml	21	12
	50mg/ml	22	14
	250mg/ml	122	47
	500mg/ml		
	750mg/ml		
Broth			
	5mg/ml	38	17
	50mg/ml	75	16
	250mg/ml	47	15
	500mg/ml		
	750mg/ml		

Icodextrin v Burkolderia cepacia

		Mean	se
Saline			
	5 mg/ml	4	4
	50mg/ml	-1	5
	250mg/ml	-41	6
Broth			
	5mg/ml	-2	5
	5mg/ml	-16	7
	250mg/ml	-74	6

Mannitol v Burkolderia cepacia

		Mean	se
Saline			
	5mg/ml	24	10
	50mg/ml	166	62
	250mg/ml	873	233
Broth			
	5mg/ml	4	4
	50mg/ml	-2	4
	250mg/ml	63	10

*se = standard error

P36200WO.3

CLAIMS

1. A pharmaceutical composition suitable for the treatment of a respiratory disorder comprising an effective amount of dextrin.

2. A pharmaceutical composition according to claim 1 characterised in that the composition comprises a polysaccharide a substantial portion of which is dextrin.

3. A pharmaceutical composition according to Claim 2 characterised in that the dextrin is selected from those polymers described in European Patent Application No 0153 164 and/or European Patent Application No 0 115 911.

4. A pharmaceutical composition according to Claim 2 characterised in that the composition comprises a dextrin mixture, said mixture including more than 15% by weight of dextrin of D.P. greater than 12.

5. A pharmaceutical composition according to Claim 4 characterised in that the mixture including more than 50% by weight of glucose polymers of D.P. greater than 12.

6. A pharmaceutical composition according to Claim 5 characterised in that the mixture contains from 5 to 75% by weight of glucose polymers of D.P. greater than 12.

7. A pharmaceutical composition according to Claim 6 characterised in that the mixture contains 75 to 100%, by weight of glucose polymers of D.P. greater than 12.

8. A pharmaceutical composition according to Claim 1 characterised in that the weight average molecular weight of the polymer mixture is from 3,000 to 75,000.

9. A pharmaceutical composition according to Claim 8 characterised in that the weight average molecular weight of the polymer mixture is from 18,000 to 22,000.

10. A pharmaceutical composition according to Claim 1 characterised in that the polymer is administered in the form of an aqueous solution.

11. A pharmaceutical composition according to Claim 10 characterised in that the aqueous solution contains at least 0.1% by weight of a glucose polymer mixture.

12. A pharmaceutical composition suitable for administration by way of a pressurised aerosol comprising a pharmaceutical composition according to claim 1 in admixture with a suitable propellant.

13. A pharmaceutical composition suitable for administration by way of a dry powder formulation comprising a pharmaceutical composition according to claim 1 optionally in admixture with a suitable adjuvant, diluent or carrier.

14. A pharmaceutical composition according to Claim 13 characterised in that the particle size of the polymer is 10 microns or less.

15. A pharmaceutical composition according to claim 14 characterised in that the composition is encapsulated in a microcapsule consisting of a biocompatible wall material.

16. A pharmaceutical composition suitable for administration by way of a nebuliser comprising a solution or a suspension of a pharmaceutical composition according to claim 1.

17. A pharmaceutical composition according to Claims 12, 13 or 16 characterised in that the dosage of pharmaceutical composition administered to a patient is in the range of from 1 mg to 10 g per metered dose or actuation.

18. A method of treating a respiratory disorder which comprises the administering of a therapeutically effective amount of dextrin to a patient suffering from such a disorder.

19. A method of treating CF which comprises administering of a therapeutically effective amount of dextrin to a patient suffering from such a disorder.

20. The use of dextrin in the manufacture of a pharmaceutical composition for the treatment of respiratory disorders.

21. The use of dextrin in the manufacture of a pharmaceutical composition for the treatment of respiratory disorders.

22. A pharmaceutical composition substantially as described with reference to the accompanying examples.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/02887

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/715 A61K31/718 A61P11/00 A61K9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, EMBASE, SCISEARCH, CHEM ABS Data, BIOSIS, PASCAL, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 48476 A (MARTIN GARY PETER ;GLAXO GROUP LTD (GB); ZENG XIAN MING (GB); LARH) 30 September 1999 (1999-09-30) page 10, paragraph 1; claims 23,25; table 6	1,2, 10-22
X	DATABASE WPI Section Ch, Week 199741 Derwent Publications Ltd., London, GB; Class B04, AN 1997-436117 XP002183546 & CN 1 116 053 A (TAN R), 7 February 1996 (1996-02-07) abstract	1,2,18, 20-22
Y		3-17,19

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 November 2001	03/12/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Uiber, P

In tional Application No
PCT/GB 01/02887

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 01141 A (UNIV BRITISH COLUMBIA ;UNIV ALBERTA (CA)) 14 January 1999 (1999-01-14) cited in the application claims 1-13	1-22
Y	FENG W ET AL: "Improved clearability of cystic fibrosis sputum with dextran treatment in vitro" AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, AMERICAN LUNG ASSOCIATION, NEW YORK, NY, US, vol. 157, no. 3, 1 March 1998 (1998-03-01), pages 710-714, XP002084086 ISSN: 1073-449X * abstract; p.714 *	1-22
A	US 4 673 633 A (KELLEHER THOMAS J ET AL) 16 June 1987 (1987-06-16) claims 1-20	1-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 01/02887

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			WO	9948476	A1	30-09-1999
			EP	1063968	A1	03-01-2001
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			WO	8600343	A1	16-01-1986